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International genetic testing

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Significant efforts are underway in the United States and abroad to ensure the safe and effective use of genetic tests. By its very nature, the integration of genetics into clinical and public health practice is international in scope. Epidemiologic data from diverse populations in many regions of the world are being collected to determine genetic contributors to disease and which populations are at increased risk. For common genetic diseases or conditions, at-risk populations exist in many countries, and genetic testing for patients and their relatives is anticipated to be widely available in numerous laboratories (e.g., cystic fibrosis carrier screening in the Caucasian population). In contrast, for rare genetic conditions, testing may be available from very few laboratories, necessitating specimen and patient referrals across national boundaries. International referral of specimens occurs, particularly for testing associated with rare diseases. Therefore, it is important for clinical practitioners, laboratorians, and those who monitor and regulate genetic testing to consider the implications of such referrals in terms of test requisition, specimen transportation and handling, reporting practices, quality assurance, and ethical, social, and legal standards.

AVAILABILITY OF MOLECULAR GENETIC TESTING LABORATORY DATABASES

Out-of-country referrals will likely increase as a consequence of raised awareness of expertise and specialty services located in diverse countries and the evolving need for patient samples to perform research and validate clinical testing protocols. Resources are available to clinical practitioners in identifying genetic testing laboratories both domestically and internationally. In the United States, GeneTests and the University of California at San Diego UCSDW3BG Biochemical Genetics database represent two major US resources to which clinical providers and researchers can find both US and non-US genetic laboratory listings.[1,2]

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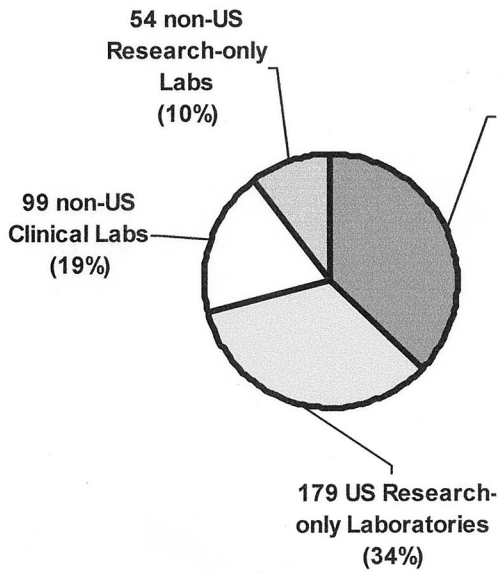
Participation in these databases is voluntary, and as such we cannot assess to what extent participation is representative of all laboratories. GeneTests is federally funded and includes an international directory of laboratories offering clinical and research genetic testing; it is maintained by the University of Washington School of Medicine, Seattle, Washington. The UCSDW3BG is maintained by the Department of Pediatrics at the University of California at San Diego in association with the Society for Inherited Metabolic Disorders. Clinical laboratories are those that return results intended for patient management, whereas research laboratories primarily focus on collecting data for scientific and clinical discovery. Differentiation between clinical and research activities can be difficult, particularly for those research activities in which individual test results are returned to the patient or health care provider and used in clinical management. In October 2002, GeneTests listed 375 US and 153 non-US laboratories (Fig. 1). Among these, 30 countries were represented. Canada has the most listings of non-US laboratories, 36, of which 23 offer clinical testing. Of non-US laboratories, 93 offered clinical services, whereas 60 of the laboratories participated only in research activities and had no clinical activities listed. Likewise, the UCSDW3BG database included 96 laboratories with 32 located outside the United States (Fig. 1). The UCSDW3BG does not differentiate between clinical and research activities. Another international laboratory database, the European Directory of DNA Diagnostic Laboratories, lists 331 laboratories from 17 European countries.[3] Country–specific laboratory registries are sometimes available as well. As these and other resources become known, questions are raised regarding the standards and definitions that various countries abide by in referring, collecting, and testing patient specimens either for clinical or research purposes.

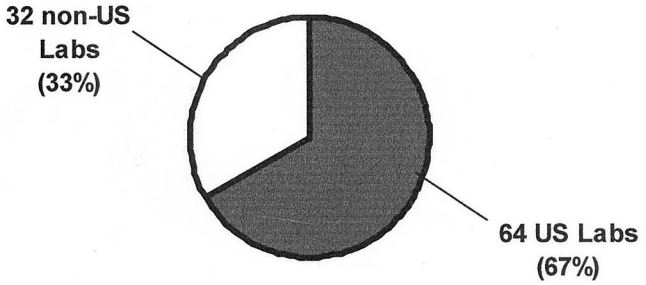
ASSURING THE QUALITY OF GENETIC TESTING IN THE UNITED STATES

In the United States, both professional organizations and governmental authorities have played important roles in ensuring the quality of genetic testing services. For example, the American College of Medical Genetics (ACMG) has developed several policy and guidance statements relevant to the clinical application of genetics.[4] Similarly, the College of American Pathologists (CAP) promotes excellence in laboratory practice through a variety of programs including their laboratory accreditation program.[5,6] This program evaluates laboratories against a "checklist" containing items intended to assure qual-

GeneTests Laboratory Database



UCSD Biochemical Laboratory Database



Summary of non-US Laboratory Participation in GeneTests

Countries	Total	Clinical Listed
Argentina	4	4
Australia	4	1
Belgium	5	3
Brazil	1	1
Canada	36	23
Chile	1	1
Cyprus	2	2
Czech Republic	2	1
Denmark	4	3
Finland	1	0
France	10	5
Germany	15	12
Greece	1	1
Israel	7	4
Italy	8	5
Japan	8	2
Korea	1	1
Mexico	2	1
New Zealand	2	2
Portugal	1	3
Russia	1	1
Saudi Arabia	1	1
Scotland	1	0
Singapore	1	1
Spain	5	5
Sweden	1	1
Switzerland	5	5
The Netherlands	6	4
Turkey	1	1
United Kingdom	16	5
Total	153	99

Fig. 1 Participation of laboratories in databases developed in the United States as of October 2002. Numbers of laboratories participating in the GeneTest and UCSD database are indicated. Laboratories described under GeneTests are further divided into those offering clinical services and those only performing research studies.

ity in laboratory practice. This program has achieved international status with 42 non-US laboratories representing 14 participating countries using the molecular pathology checklist (personal communication, Virginia Emmons, CAP, 2002). These professional organizations provide recommendations to their constituencies and serve as a forum by which voluntary standards are developed in a timely manner. Although the professional organizations do not have statutory authority, their activities influence the development of regulations and standard-of-care practices.

In addition to these voluntary standards and guidelines, national regulations also exist that provide minimum standards for assuring quality in clinical laboratory practice. In the United States, the Clinical Laboratory Improvement Amendments of 1988 (CLIA), administered by the Center for Medicare and Medicaid Services (CMS) with technical support from the Centers for Disease Control and Prevention (CDC), is a regulation applicable to all laboratories that examine human specimens and report patient-specific results for the diagnosis, prevention, or treatment of any disease, impairment, or assess-

ment of health.[7,8] The CLIA regulations specify provisions for the laboratory's operating environment, personnel standards, proficiency testing, quality control, and quality assurance. State programs may apply for CLIA exemption, providing they have regulations in place that meet or exceed the CLIA requirements. At present, New York and Washington State programs are CLIA exempt. These regulations do not apply to laboratories that test human samples and do not report patient specific results. For such research, approval is often required from an institutional review board or similar entity, and participants donating samples may be required to provide consent. In addition to the requirement that all clinical laboratories be certified under CLIA, laboratory testing devices, kits, and their components that may be used in clinical practice are subject to oversight under the Federal Food, Drug, and Cosmetic Act.[9,10] Specifically, testing devices and tests that are packaged and sold as kits to multiple laboratories require premarket approval or clearance by the Food and Drug Administration (FDA). Presently, most genetic tests are developed in-house for the laboratory's own uses and are not subject to FDA reviews. However, components of these tests are subject to the Analyte Specific Reagents Rule, which subjects reagent manufacturers to certain general controls, such as good manufacturing practices.[11]

Several groups in the United States, including the Task Force on Genetic Testing and the Secretary's Advisory Committee on Genetic Testing (SACGT), have recommended that the CMS, CDC, and FDA work together to consider, develop, and implement additional oversight to ensure effective and safe use of genetic testing.[12,13] In formulating their recommendations, the Task Force and the SACGT articulated the need to address implications related to the predictive power of genetic tests and the impact of test results for family members and at-risk populations. As one result of these deliberations, the Clinical Laboratory Improvement Advisory Committee (CLIAC) has developed a set of recommendations for developing a genetic specialty under CLIA.[14] The genetic specialty, if implemented, would provide specific requirements applicable to genetic testing not otherwise covered under the general provisions of CLIA. Most recently, the Secretary's Advisory Committee on Genetics, Health, and Society was established to replace the SACGT and in so doing address the broader implications resulting from the development and application of genetic technologies.[15]

ASSURING THE QUALITY OF GENETIC TESTING INTERNATIONALLY

Other international professional organizations and countries are active in formulating policies and recommendations applicable to genetic testing.[16] In 2000, the Organization for Economic Cooperation and Development (OECD) provided a summary from a workshop that addressed genetic testing issues pertaining to policies among its 30 member countries.[17–19] Likewise, the Public and Professional Policy Committee working group of the European Society of Human Genetics (ESHG) reported on these issues as well.[20–22] ESHG is comprised of individuals, institutions, and companies and is funded by member dues.[23] The International Federation of Human Genetics further serves to facilitate communication and collaboration among professional societies, although this group is not involved in policy development per se.[24] To facilitate best laboratory practices, the European Thematic Network for Cystic Fibrosis (CF-Network) and the European Molecular Genetics Quality Network (EMQN), both projects originally funded by the European Union, have supported external quality assessment schemes and development of "best-practices" protocols through the consensus process among its international participants (Project numbers, CF-Network: BMH4-CT96–0462, QLK3-CT99–0241; EMQN:SMT4-CT98–7515).[25–28] The EMQN is now supported by user subscription fees as of April 2002. Although the CF-Network and the EMQN are not organizations with legal identities, their international efforts and outcomes may impact laboratory quality assurance issues. Over 400 laboratories located in more than 30 countries participate in these networks.[28] Thus, there has been wide acknowledgment among the international community that genetic testing requires additional measures to assure quality in laboratory practices and that this can be achieved by a combination of enhanced regulatory oversight, adherence to recommendations developed by professional organizations, and participation in voluntary quality assurance programs. Other groups have developed policy statements as well. These include the Council of Europe, the Human Genetics Society of Australasia (HGSA), and the World Health Organization (WHO). The Council of Europe is an international organization comprising 44 member countries and is funded by member states in proportion to their population and resources.[29] HGSA is comprised primarily of the Australasian countries.[30] WHO is a specialized agency of the United Nations with 191 member countries.[31] Recently, WHO released a report of "Genomics and World Health" that describes the expectations, concerns, and possibilities for the science of genomics to improve world health.[32] No regulations yet exist in Central or South American countries that are specific for genetic testing. However, the Latin American Human Genetic Network has been established to exchange information and improve the quality of genetic services offered.[33]

In summarizing issues being addressed internationally, it is useful to differentiate between organizational recommendations and country-specific efforts. We can further differentiate between laboratory practice-specific and patient-management issues (Tables 1,2).

Laboratory practice issues include the following:

- Definition: an accepted description of genetic testing.
- Certification/Accreditation: our definitions were derived from those used by the International Laboratory Accreditation Cooperation.[34] Certification refers to a statement provided by a third party attesting to the fact that an organization meets certain standards. Accreditation is the independent assessment of the technical competence and quality systems of an organization. Because the application of these terms varies among the international com-

Table 1
Issues addressed by international governmental/professional groups

Issue	Council of Europe	OECD	ESHG	EMQN	HGSA	WHO
Laboratory practice						
Definition	*	*	*		*	*
Certification/accreditation	*	*	*	*	*	
Personnel standards	*		*		*	
Quality assurance	*	*	*	*	*	
Quality control		*	*	*	*	*
External quality	*	*	*	*	*	
Assessment						
Clinical validity		*	*		*	
Analytic validation		*	*			
Record retention		*				*
Reporting				*	*	
Referral standards	*	*	*			
Total issues addressed	6	9	9	5	8	3
Patient management						
Informed consent	*	*	*	*	*	*
Counseling	*	*	*		*	*
Use of residual samples	*	*	*	*	*	*
Privacy/confidentiality	*	*	*	*	*	*
Access to services	*	*	*			*
Education	*	*	*		*	*
Total issues addressed	6	6	6	3	5	6

*Indicates issues being addressed.
OECD, Organization for Economic Cooperation and Development; ESHG, European Society for Human Genetics; EMQN, European Molecular Genetics Quality Network; HGSA, Human Genetics Association of Australia; WHO, World Health Organization.

munity, we chose not to differentiate between certification and accreditation in this report. Both government and private bodies certify and accredit among the international community, but these practices vary by country. For instance, in the United States, CLIA does not accredit laboratories, but accreditation is provided by nongovernment accrediting organizations to meet federal certification requirements. We did not assess the rigor to which standards are applied in providing certification or accreditation.

- Quality assurance refers to "a system of activities whose purpose is to provide assurance that the overall quality-control job is being done effectively."[35]
- Personnel standards: education and training specified for the laboratory director and technical staff.
- Quality control: "the overall system of activities whose purpose is to provide a quality of product or services that meets the need of users."[35]
- External quality assessment (also known as proficiency testing): a comparison of laboratory performance against an agreed-upon independent standard.
- Clinical validity: how well a test predicts the presence or absence of a clinical condition or predisposition.[14]
- Analytic validation: a mechanism to establish the analytic validity of a test before its clinical offering.
- Record retention: the preservation of records about each test performed or its results.
- Reporting: conveying of the test result and interpretation to the referring entity.
- Referral standards: advice provided by the laboratory regarding follow-up testing.

Patient management issues include the following:

- Informed consent: a formal process in which the benefits and risks of the test are described to and understood by the patient before the decision to be tested is made.
- Counseling: advice regarding the provision of genetic counseling to either the patient or family members.
- Use of residual samples: the disposition of excess patient-derived materials.
- Privacy/confidentiality: protections in place to assure appropriate access and use of patient information.
- Access to services: access of persons or populations who may benefit from genetic testing services.
- Education: establishing or maintaining competency in the provision of genetic testing services, as appropriate.

Although this list is not comprehensive, in considering these issues, we can highlight several important international efforts.

Internet resources and publications were readily accessible sources in reviewing these issues. Of the international organizations listed, many common issues are addressed (Table 1). However, approximately one third did not have provisions that addressed analytic validation, record retention, or reporting practices. WHO places emphasis on access to testing services and the accompanying ethical, legal, and social issues. The EMQN addressed issues consistent with its role in supporting laboratory assessments and best-practices meetings, emphasizing the analytic phase of laboratory testing. Although the OECD addressed the majority of the issues specified, this group placed less emphasis on personnel standards and test reporting requirements. Many of these efforts are complementary and together encompass a great number of important issues.

Many countries have regulations in place or are developing recommendations for regulations that specifically address genetic testing. These are sometimes difficult to fully summarize because some regulations may not occur under the genetic heading. In looking at efforts within a few select countries, the United States (CLIA/CLIAC), Australia, Austria, Canada, France, Germany, the Netherlands, and the United Kingdom, we can highlight some of the major issues being addressed (Table 2). The Canadian College of Medical Genetics has adopted policies on which some of the more local provincial efforts are in part based. In four of these countries (United

Table 2
Issues addressed in selected countries

Issue	CLIA (reg)[7,8]	CLIAC (rec)[14]	Australia (reg)[46,47]	Austria (reg)[48]	France (reg)[49]	Canada (rec)[50]	Germany (rec)[51–53]	Netherlands (rec)[54]	United Kingdom (rec)[55,56]
Laboratory practice									
Definition		*	*	*	*	*	*	*	*
Certification/accreditation	*	*	*	*	*	*		*	*
Personnel standards	*	*	*	*	*	*	*		
Quality assurance	*	*	*		*	*	*	*	*
Quality control	*	*	*	*	*	*	*	*	*
External quality		*	*		*	*	*		*
Assessment									
Clinical validity		*	*				*		*
Analytic validation	*	*	*		*		*	*	*
Record retention	*	*	*		*				*
Report requirements		*	*			*	*		
Follow-up testing		*		*	*	*			*
Total issues addressed	6	11	10	5	9	8	8	5	9
Patient management									
Informed consent		*	*	*	*	*	*	*	*
Counseling	*	*	*	*	*	*	*	*	*
Use of residual samples		*			*	*		*	*
Privacy/confidentiality	*	*	*	*	*	*	*	*	*
Access to services			*					*	*
Educational component			*		*	*	*		*
Total issues addressed	2	4	5	3	5	5	4	5	6

*Indicates issues being addressed either through recommendation (rec) or regulation (reg), as indicated.
CLIA, Clinical Laboratory Amendments of 1988; CLIAC, Clinical Laboratory Improvement Advisory Committee.

States, Australia, Austria, and France), regulatory requirements (along with mechanisms for developing additional recommendations) have been developed, whereas in four others, (Canada, German, The Netherlands, and United Kingdom) only recommendations exist. Issues not uniformly addressed among these countries include external quality assessment (proficiency testing), establishing clinical validity, record retention, and test result reporting requirements. Almost all countries considered informed consent, counseling, and confidentiality issues. In some countries, such as the United States, professional organizations such as ACMG and CAP provide voluntary quality assurance standards, guidelines, and recommendations important in augmenting the minimum standards set by regulations. Testing for acquired mutations was not usually included under the category of genetic testing, and several countries included guidance with regard to education and delivery of services to ensure the quality and access of genetic testing services.

Many similar issues are being considered among international and professional organizations and individual countries. However, there appears to be a lack of uniformity among professional bodies in addressing certification/accreditation, analytic validation, and test result reporting. Although accreditation exists within several countries, an internationally recognized accreditation system for genetic testing laboratories does not yet exist. It is important to note that although the international groups reviewed herein do not accredit laboratories, their recommendations may encourage groups that do accredit to extend their efforts into the field of genetics. The issue of internationally accepted accreditation can assume importance by providing a mutually agreeable measure of competence and quality. This can be useful for laboratories wanting this level of recognition and to clinical practitioners as an assurance of quality of service offered. Indeed, it has been shown in a survey of molecular genetic testing laboratories in the United States that the accreditation status of the laboratory correlated in a positive way with quality assurance practices.[36] To facilitate cross-country acceptance of test data in a number of fields, several international groups have been established to promote compatible and mutually acceptable accreditation schemes. Among these are the National Cooperation for Laboratory Accreditation (US), the European Cooperation for Accreditation (European Union), and the International Labora-

tory Accreditation Cooperation (serving various accreditation schemes operating throughout the world).[37–39] As genetic testing accreditation schemes develop and mature, these regional and global efforts may prove useful in promoting harmonization and trust among the international community. We noted a lack of distinction in terminology referring to certification and accreditation. Adoption of a common understanding of terms within the international community will be useful for both laboratories and those that refer tests. The impact of national laboratory licensing requirements can be difficult to evaluate because licensing does not necessarily require laboratories to meet certain standards or demonstrate competence, as does certification and accreditation.

Aside from regulatory mandate, another mechanism to facilitate adoption of common standards is through voluntary means. As such, the EMQN and the CF-Network have advocated the consensus development of "best-practice" guidelines that provide guidance to genetic laboratories about analytical issues, as well as reporting and interpretation of genetic test results. Similarly, NCCLS, a globally recognized, voluntary consensus–standards-developing organization, developed several comprehensive technical standards for specific areas, including one for molecular diagnostic methods for genetic diseases.[40] These efforts are of great importance, but they face challenges in light of rapidly changing technologies and the need to regularly review, update, and distribute new guidelines. In addition, the existence of professional standards and recommendations do not provide any assessment of the actual quality of testing, which is best assessed through external quality assessment (proficiency testing) programs.

Programs developed under CAP, the European CF-Network, and the EMQN serve an international audience and strive to improve the practice of laboratory medicine by identifying analytic errors and their causes and correcting problems by educating the laboratories.[6,25,26,28,41] Indeed, a progressive reduction in the percentage of laboratories making genotyping errors was observed in analyzing results from the European CFTR (cystic fibrosis) external quality assessment scheme from 1996 through 2000.[42,43]

Equally important to ensuring quality in genetic testing is addressing the postanalytic issues such as result reporting. Several US professional organizations and CLIAC made recommendations on report format and content. Similarly, the EMQN developed a draft consensus document that addresses the reporting of genetic test results. Nevertheless, studies show significant variation in reporting practices and differences in comprehension of reports by physicians, suggesting the need for further guidance.[44,45] These issues are likely amplified when reports cross national and cultural boundaries.

At this time, we cannot comment on the extent to which policies and recommendations are implemented and followed. Establishing a useful and acceptable balance between voluntary participation in quality assurance programs and regulatory mandates is a sensitive issue. It is important to recognize that policies and practices are developed on the basis of available resources, culture, politics, and the social and business environments, and these differ among countries. Nonetheless, developing a common set of principles, where appropriate, is of value to individual countries in developing policies that not only serve the best interests of their population but are compatible with standards set in other countries. We expect that these efforts will raise the overall quality of genetic testing services and provide confidence in the quality of these services when patient samples and information are sent out of country.

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